

REMARKS

Upon amendment, Claims 19-23, 25-28 and 30-38 are pending. Claims 35-38 are withdrawn. Claims 19-34 are withdrawn in part as the Examiner has determined the elected subject matter to pertain to compounds in which n is 4 and A is thienyl. Claims 24 and 29 have been canceled without prejudice or disclaimer. Claim 19 has been amended to include the subject matter of previously elected claim 24, to recite that R⁸ is hydrogen or alkyl and to correct a typographical error. Claims 36 and 38 have been amended to correct claim dependency and claim 37 has been amended to correct a typographical error. Support for these amendments can be found throughout the specification, and in particular in at least Examples 35, 39, 40, 42 and 34. *No new matter has been added.*

Amendment and cancellation of the claims herein is not/are not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed or similar claims in this or one or more subsequent patent applications.

Claim Rejections – 35 U.S.C. § 102

Claims 19-33 are rejected under 35 U.S.C. §102(b)

Claims 19-33 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by DE 100 08 089 to Gerhard et al. (Gerhard). In particular over compound 1 on page 5 of Gerhard. Applicants respectfully disagree and traverse the rejection.

As amended, Claim 19 has been amended to recite that that R⁸ is hydrogen or alkyl. That is, the nitrogen atom next to the isopropyl group is substituted either by hydrogen or by an alkyl group. The corresponding nitrogen atom in Compound 1 on page 5 of Gerhard is substituted by the moiety –CH₂OCO–. Indeed, none of the compounds disclosed in Gerhard carry a nitrogen atom corresponding to the R⁸ substituted nitrogen of the present claims which is substituted either by hydrogen or by an alkyl group.

As such, Gerhard does not anticipate the present claims and thus Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Claims 19-34 are rejected under 35 U.S.C. §103(a)

Claims 19-34 are rejected as being allegedly unpatentable over Gerhard or over DE 196 38 870 to Reichenbach et al. (Reichenbach) in view of Chemical Abstract CA 52:93347 (1958) to Noren (Noren).

The Examiner alleges that the difference between the present claims and the prior art is that the present claims are drawn to compounds which utilize a leucine residue whereas the prior art utilizes an iso-leucine residue and that it is well known that tabulysins are isolated from culture of myxobacterial. The Examiner further alleges that Noren discloses that both leucine and iso-leucine are essential nutrients for culturing mycobacter and thus both are available to the culture media and both would be expected to exhibit analogous activity.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P. § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Four factual inquiries must be made: first, a determination of the scope and content of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject matter is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success;

and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, [Inc. v. Ficosa N. Am. Corp.]*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

As an initial comment, while the elected species carries a leucine residue, the claims are not so limited. Indeed the Examiner has described the "elected class" only as bearing a ring (as described in prior claim 24 now incorporated into claim 19), $n = 4$ and $A =$ thienyl without reference to the R^6 and R^7 definitions. Indeed, the elected compound is merely representative of those generically claimed.

Applicants respectfully submit that neither Gerhard or Reichenbach render the claimed invention obvious. In particular, Applicants note that neither Gerhard nor Reichenbach disclose compounds in which the nitrogen atom corresponding to the claimed $N-R^8$ moiety is substituted either by hydrogen or by an alkyl group. Indeed, all tubulysin derivatives known in the prior art carry a group of formula $-CH_2OCO-$ at position R^8 . As such, Applicants contend that prior to the instant invention, one of ordinary skill in the art would have expected that this group is essential for the activity of the tubulysins. Indeed, this is confirmed as both Gerhard and Reichenbach only disclose compounds bearing a $-CH_2OCO-$ group at the corresponding position. As such, one of ordinary skill in the art would have had no motivation to modify the compounds of Gerhard or Reichenbach at the R^8 position.

Furthermore, Applicants respectfully submit herewith a declaration signed by Dr. Wolfgang Richter, the managing director of the assignee R&D-Biopharmaceuticals.

This declaration contains a table wherein the IC-50 data against different cell lines are shown for compounds wherein R⁸ is either hydrogen or methyl. This data is compared with the data for naturally occurring tubulysins A and D (each of which bear a -CH₂OCO- group). This data clearly shows that the derivatives having hydrogen or a methyl group at R⁸ show a similar activity as the natural tubulysins A or D. Since all tubulysin derivatives known prior to the present invention were carrying a group of formula -CH₂OCO-, at position R⁸. One of ordinary skill in the art, in light of the steric and electrochemical differences between this group and a hydrogen or alkyl group, would not have had any reasonable expectation that these compounds would have similar activity.

Finally, nothing in Noren remedies the deficiencies of Gerhard or Reichenbach. Applicants respectfully note that myxobacteria described by Noren is a very broad genus for a great variety of bacteria. Noren does not disclose the bacteria *Archangium gephyra*. Further, as disclosed on page 4 of DE 196 38 870, no single amino acids are used for the fermentation but only a complete protein. Therefore, Applicants respectfully assert that even if the differences between Gerhard or Reichenbach and the claimed invention were a single amino acid residue, which Applicants have shown above is not the only difference, Applicants believe that the Noren reference would not be considered relevant to Gerhard or Reichenbach by one of ordinary skill in the art. That is to say, one of ordinary skill in the art, in light of the deficiencies of Noren, would have had no motivation to combine Noren with Gerhard or Reichenbach .

In sum, neither Gerhard or Reichenbach, alone, nor in combination with Noren, teach or suggest the claimed compounds, and thus the rejections of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Rejoinder of Method Claims

Claims 35-38 relate to methods of treating a patient comprising one or more compounds of claim 19. As such, method of use claims 35-38 are commensurate in scope with the present compound claims. Since a search for the compounds of claim

19 will necessarily result in all uses of any such compounds, and as Applicants believe that claim 19 is presently in a condition for allowance, Applicants respectfully request rejoinder of method of use claims 35-38 in accordance with M.P.E.P. 821.04 and In re Ochiai, 71, F.3d 1565 (Fed. Cir. 1995).

CONCLUSION

In view of the amendments and remarks made herein, Applicants submit that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If a telephone conference with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number indicated below.

FEE AUTHORIZATION

Applicants authorize the Director to charge the extension fee and any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 62661(52171).

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